DETAILED ACTION

Request for Continued Examination

A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on 02/09/2011 has been entered.

Status of Application/Amendment/Claims

Applicant's response filed 02/09/2011 has been considered. Rejections and/or objections not reiterated from the previous office action mailed 11/09/2010 are hereby withdrawn. The following rejections and/or objections are either newly applied or are reiterated and are the only rejections and/or objections presently applied to the instant application. The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

Claims 111-113 are currently under examination. **No claims are allowable.**

New Claim Rejections

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained through the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 111-113 are rejected under 35 U.S.C. 103(a) as being unpatentable over Abe et al. (European Journal of Pharm. Sci, 2001 of record IDS filed 09/12/2005), Tuschl et al. (WO 02/44321 of record), Astriab-Fisher et al. teach (Biochemical Pharmacology, 2000. Vol. 60, pp.83-90 of record), Lee et al. (Molecular Therapy 2001, Vol. No. 4, No. 4: 339-346) and evidenced by Caplen (Expert Opin. Biol. Ther. 2003, 3(4): 575-586 of record).

The claims are drawn to methods of inhibiting a transcript associated with a influenza virus, or methods of treating an influenza virus nucleoprotein or a clinical condition associated with overexpression or inappropriate expression of an influenza transcript, comprising administering an siRNA in combination with a cationic peptide, and wherein said administration is vascular.

Abe et al. teach targeting an antisense compound to a gene encoding the influenza viral nucleoprotein (NP). Abe et al. teach sequence specific inhibition of expression in vitro using said antisense compounds delivered using liposomes (see Table 2). Abe et al. teach intravenous delivery of antisense compounds to mouse infected with influenza virus and teach a reduction in the viral target mRNA and a decrease in virus titer in the lungs (see pages 65-68). Abe et al. do not teach using a siRNA targeted to a viral nucleoprotein or teach using a siRNA and a cationic peptide.

Tuschl et al. teach the use of siRNA compounds to inhibit gene expression. Tuschl et al. teach siRNA are the new alternative to antisense compounds and have

improved efficacy and safety (see page 3). Tuschl et al. teach a method of using siRNA to infect cells of mammals and teach modulating of the function of a target gene in numerous tissues and cells, such as a viral target gene (see page 8). Tuschl et al. teach the siRNA can be delivered using a carrier system (see page 8) and teach the siRNA can be administered by injection. Additionally, Tuschl et al. teach a vector capable of expression of a siRNA (see page 7).

Astriab-Fisher et al. teach inhibition of gene expression using oligonucleotides conjugated to cationic peptides. Astriab-Fisher et al. teach one of the major problems with the use of oligonucleotides is delivery to the cytoplasm and nucleus of the cells and teach it was known in the art to try and overcome this problem by complexing the oligonucleotide with liposomes but one major liability with this approach is that liposomes do not work well in the presence of serum and therefore are not effective in vivo situations (see page 83). Astraib-Fisher et al. teach the use of delivery cationic peptides such as Tat protein and Antennapeida protein which are capable of intracellular delivery of molecules across cell membranes (see page 83-85).

Lee et al. demonstrates methods of intravenous delivery of a composition comprising an antisense nucleic acid molecule complexed with a polylysine (PLL) into a mouse wherein the antisense complex is capable of reducing target gene expression (see at least page 342).

It would have been obvious to one of skill in the art to substitute a siRNA molecule for the antisense molecule in the method of inhibiting an influenza viral gene

taught by Abe et al. It would have further been obvious to use the cationic peptide to efficiently deliver the siRNA to the cell of interest.

It was well known at the time of the instant invention that silencing of gene expression using siRNA was more efficient and sequence specific as compared to antisense or ribozyme technologies. One of ordinary skill in the art would have clearly substituted the antisense compound taught by Abe et al. with a siRNA in a method of inhibiting an influenza viral gene expression in infected organs of a subject. Therefore, because as demonstrated by Tuschl et al., siRNAs were known to be more efficient at silencing gene expression, one of ordinary skill in the art at the time the invention was made would have clearly substituted the antisense molecule for a siRNA to target the influenza viral NP gene.

It was further well known at the time of filing that that one of the major problems with the use of oligonucleotides is delivery to the cytoplasm and nucleus of the cells and that siRNA has the same delivery issues as antisense oligonucleotides (as evidenced by Caplen Expert Opin. Biol. Ther. 2003, 3(4): 575-586) who states "[m]any of the problems associated with developing RNAi as an effective therapeutic are the same as encountered with previous therapy approaches. The key issues of delivering nucleic acids to the required tissue and cell type, while ensuring an appropriate level of efficacy with minimum toxicity induced by the vector system, have been problems the gene therapy field has struggled with for over a decade now" see page 581, last paragraph).

It was also well known in the art that using peptide-nucleic acid complexes could overcome these problems and therefore one of ordinary skill in the art would have used

a delivery agent as taught by Astriab-Fisher et al. Lee et al. demonstrates that an antisense inhibitory compound complexed to a peptide was capable of being delivered intravenously and inhibited expression of a target gene.

Given that Abe et al. demonstrates proof of principle of delivery of inhibitory nucleic acid to the respiratory system via intravenous administration using liposomes, the skilled artisan would have clearly been motivated to use this method substituted with a more efficient inhibitory nucleic acid such as siRNA and substituted with a more efficient and efficacious delivery agent for in vivo therapeutic use such as a peptide for treatment of influenza.

There would have been a reasonable expectation of success at using a peptide for delivery of a siRNA into cells, given Astriab-Fisher et al. and Lee et al. teach delivery of a nucleic acid to cells and in vivo using a peptide carrier.

Thus in the absence of evidence to the contrary, the invention as a whole would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made.

Response to Arguments

Applicant's arguments filed 02/19/2011 have been fully considered but they are not persuasive. Applicant argues Abe teaches away from the claimed methods involving non-encapsulated nucleic acids. Applicant argues Tuschl makes no mention of delivery to the respiratory system and does not mention vascular administration such that the nucleic acid is delivered to the respiratory system and in addition Astriab-

Fischer describes in vitro cell culture experiments and does not mention vascular administration. Applicant also states that Caplen is not available as prior art and one of skill in the art would not understand it to render obvious the claims.

Applicant arguments with respect to Herweijer and Trubetskoy are moot as these references were not used in the new grounds of rejection above.

In response to applicant's arguments against the references individually, one cannot show nonobviousness by attacking references individually where the rejections are based on combinations of references. See *In re Keller*, 642 F.2d 413, 208 USPQ 871 (CCPA 1981); *In re Merck & Co.,* 800 F.2d 1091, 231 USPQ 375 (Fed. Cir. 1986).

With respect to Abe et al., this reference was cited for teaching inhibition of influenza viral nucleoprotein expression using a nucleic acid such as antisense compound delivered intravenously using a liposome carrier. Abe et al. teach a reduction in the viral target mRNA and a decrease in virus titer in the lungs and highlights the notion that inhibitory nucleic acids may be a viable therapeutic treatment against influenza virus. While it is true that Abe et al. do not teach the use of peptides for delivery of inhibitory nucleic acid molecules to a target gene, Abe et al. clearly recognized the importance and capability of targeting the expression of influenza virus for therapeutic treatments and the skilled artisan at the time of filing would have looked to Abe et al. for such treatments and would have further substituted siRNA for antisense given all that was known in the art regarding siRNA as a more potent inhibitory nucleic acid molecue as taught by Tuschl et al.

Moreover, while Tuschl et al. do not teach the claimed delivery agents, it was well known in the art that siRNA has the same delivery issues as antisense oligonucleoitdes and thus it would have been obvious to use a delivery agent to deliver siRNA in vivo.

Abe et al. demonstrates proof of principle of in vivo delivery of nucleic acids using liposome administered intravenously and because it was clear that liposomes suffered from suspectibility to degradation or inefficiency in serum and thus would not be an effective delivery agent as taught by Astriab-Fisher et al., one of skill in the art would have looked for a more efficient delivery agent. It was also well known in the art that using peptide-nucleic acid complexes could overcome these problems and demonstrated by Lee et al. that small nucleic acid molecules could in fact be complexed to a peptide and delivered intravenously to a target cell to reduce target gene expression. Therefore one of ordinary skill in the art would have used a peptide delivery agent as taught by Astriab-Fisher et al. to deliver siRNA in vivo for therapeutic treatments of inhibition of influenza virus.

Caplen, while not prior art, is evidence of the state of the art with respect to delivery of siRNA molecules and therefore one of skill in the art was aware of the delivery issues of siRNA at the time of filing and would have clearly used a more efficient delivery method given siRNA are nucleic acids just as antisense and are plagued with the same delivery and stability issues in vivo.

Thus the invention as a whole would have been obvious at the time of filing based on the combination of references above.

Double Patenting

The rejection of claims 111-113 remain provisionally rejected under the judicially created doctrine of double patenting over claims 12, 22 and 24-27 of copending Application No. 11/259,434.

No claims are allowable.

Conclusion

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Kimberly Chong whose telephone number is 571-272-3111. The examiner can normally be reached Monday thru Friday between 7-4 pm.

If attempts to reach the examiner by telephone are unsuccessful please contact the SPE for 1635 Heather Calamita at 571-272-2876. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

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